Low Florbetapir PET Uptake and Normal Aβ1-42 Cerebrospinal Fluid in an APP Ala713Thr Mutation Carrier

Gemma Lombardi[a], Valentina Berti[c], Andrea Tedde[a], Silvia Bagnoli[a], Irene Piacenti
Cristina Polito[b], Giulia Lucidi[a,c], Camilla Ferrari[c], Andrea Ginestroni[d], Marco More
Alberto Pupi[b], Benedetta Nacmias[a,*] and Sandro Sorbi[a,c]
[a]*Department of Neuroscience, Psychology, Drug Research and Child Health, University of F*
Florence, Italy
[b]*Department of Biomedical, Experimental and Clinical Sciences "Mario Serio", Nuclear M*
University of Florence, Florence, Italy
[c]*IRCCS Don Gnocchi, Florence, Italy*
[d]*Neuroradiology Unit AOU Careggi, Florence, Italy*

Handling Associate Editor: Daniela Galimberti

Accepted 31 January 2017

Abstract. According to the literature, the *APP* Ala713Thr mutation is associated with Alzheimer's
amyloid angiopathy. We describe a case of dementia clinically compatible with frontotemporal dementia
mutation carrier in which both [^{18}F]Florbetapir PET uptake and A$\beta_{1\text{-}42}$ cerebrospinal fluid levels w
evidences are required to establish if this association is only incidental.

Keywords: *APP* Ala713Thr, familial Alzheimer's disease, florbetapir PET, frontotemporal dementia

INTRODUCTION

The revised National Institute on Aging-Alzheimer's Association (NIA-AA) diagnostic criteria for dementia due to Alzheimer's disease (AD) encourage the use of biomarkers in order to improve AD cases identification [1], and according to International Working Group-2 diagnostic criteria, the diagnosis o presence of a pathophysiologica accuracy of amyloid positron em (PET) imaging in detecting amylo has been demonstrated [3], and s found a correlation between fluid (CSF) A$\beta_{1\text{-}42}$ levels and plaques in the brain [4] as well amyloid PET uptake [5]. In the AD causative mutation, the certa is caused by AD pathology is in

*Correspondence to: Prof. Benedetta Nacmias, Department of Neuroscience, Psychology, Drug Research and Child Health, University of Florence, Viale Pieraccini 6, 50139 Florence, Italy. Tel.: +39 055 7948910; Fax: +39 0552758265; E-mail: benedetta.nacmias@unifi.it.

ISSN 1387-2877/17/$35.00

MATERIAL AND METHODS

A 51-year-old Italian man was admitted to our clinic because of gradual change in behavior and personality, cognitive decline, and urinary incontinence; symptoms started one year before the first visit. Family history included a maternal aunt affected by unspecified early onset dementia (55 years) who died at the age of 75. No other cases of neurodegenerative/vascular dementia were known in the family. The mother died at 76 years because of renal failure in diabetes mellitus, while the father was affected by syphilis and died at the age of 78 years.

Information about health status of his cousins were not available. The patient underwent clinical-neuropsychological assessment and conventional brain magnetic resonance imaging (MRI); subsequently, since the diagnosis was uncertain, supplemental investigations on biomarkers were performed: brain [^{18}F]fluorodeoxyglucose ([^{18}F]FDG) PET, CSF analysis, genetic analysis for frontotemporal dementia (FTD), genetic analysis for FAD and lastly amyloid PET. All exams, except the amyloid PET, were carried out one year after the symptoms onset (baseline); neuropsychological evaluation was performed at baseline and at 6-month follow-up (Table 1), while amyloid PET was made 3 years after the symptoms onset.

The extensive neuropsychological evaluation was conducted with the Mini-Mental State Examination (MMSE) [10] and by tests assessing memory (Rey Auditory Verbal Learning Test [11], Babcock Story Recall Test [12], Digit Span Forward and Backward [13]), attention (Trail Making Test A and B [12]), language (Verbal Fluency [11, 14]), executive functions (Frontal Assessment Battery [15], Stroop Test [16]), visuospatial abilities (Rey–Osterrieth Complex Figure Test [17]), praxia (qualitative evaluation), mood assessment.

With regards to the genetic analy
was extracted from peripheral blo
standard procedures, by utilizing
tem (Qiagen, Hilden, Germany).
FTD causative mutations (*MAPT*,
then for FAD causative mutations
and *APP*) were performed follow
tocol [23]. The Apolipoprotein E
was determined using PCR and H
combination of the two single nu
phisms (rs429358 and rs7412) on t
Lumbar puncture and CSF colle
out according to good clinical p
ple was analyzed for total-Tau,
$A\beta_{1-42}$ by commercial enzyme-l
bent assay (innogenetics ELISA).
values were: for total-Tau <300 p
Tau <60 pg/ml, and for $A\beta_{1-42}$ >6

RESULTS

At neurological examination, s
and left hand resting tremor w
out other extrapyramidal signs. N
assessment showed significant ap
reduced verbal initiative and ve
term memory impairment, slight
functions, and functional decline
self-care deficit). The MMSE sc
reference norms (21), the Neurops
score was relatively high (28) b
delusions, severe apathy, motor
typed behaviors, dietary chang
daytime sleepiness. The clinical p
tive of early onset dementia in t
spectrum.

Trail Making Test		
A	(55")	(50")
B	73" (110")/1 Err	not evaluable
Stroop Test		
Time Interference Effect	17.5" (18)	not evaluable
Errors Interference Effect	(0)	not evaluable
Phonemic Word Fluency	6.5 (5)	11.5 (10)
Semantic Word Fluency	20.5 (19)	14.5 (13)
Neuropsychiatric Inventory	(28/144)	(40/144)
Activities of Daily Living Scale	(4/6 preserved)	(3/6 preserved)

Brain MRI showed diffuse fronto-temporo-parietal atrophy (Pasquier score was 14 and the most affected regions were the fronto-temporals) with bilateral involvement of hippocampus (Scheltens score was 3 on the right side, 2 on the left side), without evident vascular burden (Fazekas score was 1) (Fig. 1a). The MRI pattern was not suggestive for any specific dementia subtype.

Brain [^{18}F]FDG PET scan (Fig. 1b) revealed severe bilateral hypometabolism in the anterior prefrontal, anterior cingulate, medial frontal, orbitofrontal cortices, in the hippocampi, amygdala, temporal pole, and caudate nuclei (mainly on the right side). Moderate bilateral hypometabolism in the insula and posterior cingulate cortex was also evident, whereas the metabolism in the posterolateral parietal cortex was preserved. This pattern of predominantly anterior hypometabolism has been interpreted as suggestive of neurodegenerative disease not in the AD spectrum but more likely in the FTD spectrum.

With regards to CSF biomarkers, $A\beta_{1\text{-}42}$ and phospho-Tau were within the normal range (respectively, 771 pg/ml and 35 pg/ml), whereas total-Tau was slightly increased (354 pg/ml); according to current evidence, these values and their ratios were not suggestive of AD (total Tau/$A\beta_{1\text{-}42}$ value (0.46) was not suggestive of AD profile according to Duits et al. [25], phospho-Tau/$A\beta_{1\text{-}42}$ not suggestive of AD profile ac et al. [26]).

Based on these results and on diagnosis of behavioral FTD was

Genetic analysis for FTD ca (*MAPT, GRN*, C9*orf*72) was neg early onset dementia, genetic causative mutations was also perfo the occurrence of an *APP* Ala713T heterozygous mutation in the prese genotype.

Lastly, amyloid imaging wit PET was performed and no signifi retention was found (Fig. 1c). Th ease onset, the clinical picture by mutism and compulsive behav ment of attention and executive gait, and dysautonomic dysfu hypersalivation).

According to all the data, an sis of "frontal variant AD", in th causative mutation and in the ab biomarkers, has been assumed. A on the non-genetic biomarkers pr to Rascovsky's criteria [27], a cl possible FTD, behavioral variant postulated.

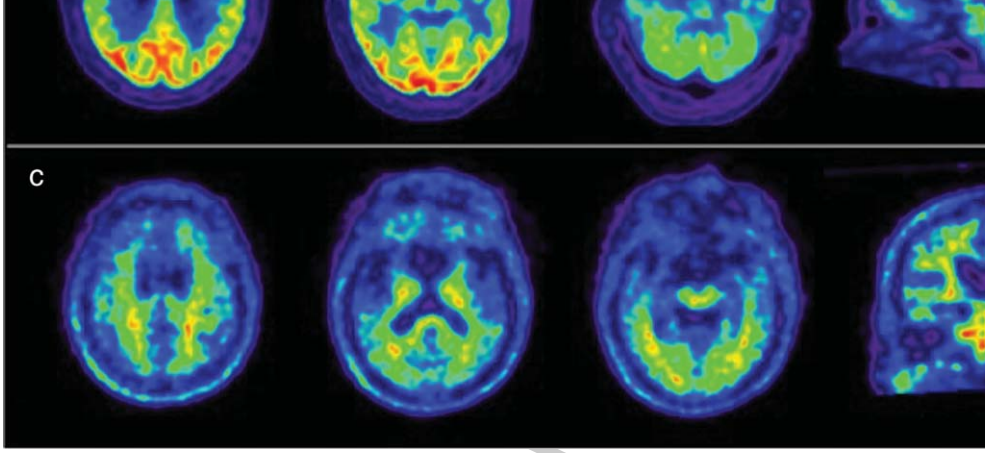

Fig. 1. Neuroimaging data a) MRI, axial T2-weighted fluid-attenuated inversion recovery images and coronal T vascular lesions, evidence of cortical and hippocampal atrophy; b) [^{18}F]FDG-PET: severe hypometabolism in fronta caudate nuclei; c) [^{18}F]Florbetapir PET: no tracer retention in grey matter.

DISCUSSION

The potential AD pathogenicity of *APP* Ala713Thr (g.275329G>A) variant is confirmed by segregation of the mutation with the disease [8, 9, 28, 29], absence of the mutation in control subjects [8, 9, 28], and results of bioinformatics analysis [30].

This variant is reported in mutation databases as pathogenic (http://www.molgen.ua.ac.be/ADmutations [31], http://www.alzforum.org/mutations [32], http://www.hgmd.cf.ac.uk/ [33]); it has been described associated with autosomal dominant FAD, with both early and late onset, and cerebrovascular lesions. Despite these considerations, asymptomatic subjects of heterozygous carriers have been reported [8, 9]; since these cases were mainly younger than 65 years [8] or than the average age at onset of respective affected family members [9], they cannot be considered spared from the disease. Moreover, an incomplete penetrance of the mu posed in order to explain this phe genetic or environmental factors for the expression/unexpression [7].

In the present case, the genetic contrast with the lack of evidence assessed by both CSF analysis a ing. Some cases of negative amyl reported in FAD in both Arctic A ers [34] and *APP* Glu693del mut also in rare sporadic cases of disea compound B PET ([^{11}C]PiB PET expected cerebral amyloid burden

PiB binding was found to be tain forms of Aβ, such as Aβ or high-affinity binding sites wh present in each amyloid plaque of [^{18}F]Florbetapir uptake in the

variant (oligomeric toxicity without alteration in Aβ ratio [37]), it is conceivable that CSF $A\beta_{1-42}$ value remains in the normal range and that CSF $A\beta_{1-40}$ (not evaluated in this case) decreases. This hypothesis is based on the evidence that the reduced Aβ-peptides in CSF match the peptides accumulated in the amyloid plaques [38].

Instead of AD diagnosis, the co-occurrence of an altered Aβ sequence with a FTD phenotype could suggest an association between *APP* Ala713Thr mutation and the FTD pathology. A causative role of *APP* Ala713Thr in pathology different from AD has not been previously supposed, whereas mutation located at the same codon (the *APP* Ala713Val) was found associated to schizophrenia with cognitive deficit [39], suggesting that mutations involving codon 713 can be pleiotropic.

In conclusion, we describe the first case of *APP* Ala713Thr mutation carrier associated to both low [^{18}F]Florbetapir PET uptake and normal $A\beta_{1-42}$ CSF. It remains to be clarified whether *APP* Ala713Thr mutation is linked to AD without *in vivo* evidence of Aβ biomarkers or more likely to other pathology as FTD, and the debate is unsolvable without histopathological examination. Based on our findings, we suggest that in the occurrence of an AD causative mutation, more than one criterion is necessary for the *in vivo* evidence of AD pathology and that pathophysiological biomarkers should be studied even in carriers of a pathogenic mutation, in order to confirm the genetic diagnosis or, alternatively, to suppose other diagnosis and the relative pathogenic mechanism.

ACKNOWLEDGMENTS

This study was supported by grants from Italian Ministry of Health RF-2010-2319722 and

265-269.

[2] Dubois B, Feldman HH, Jacova C, JL, Blennow K, DeKosky ST, Gaut man R, Cappa S, Crutch S, Engel Fox NC, Galasko D, Habert MO, Pasquier F, Rabinovici G, Robert P Sarazin M, Epelbaum S, de Souza L Schneider L, Stern Y, Scheltens P. Advancing research diagnostic crite ease: The IWG-2 criteria. *Lancet N*

[3] Herholz K, Ebmeier K (2011) Clini Alzheimer's disease. *Lancet Neurol*

[4] Strozyk D, Blennow K, White LR, Abeta 42 levels correlate with a in a population-based autopsy 652-656.

[5] Fagan AM, Mintun MA, Mach CS, Shah AR, LaRossa GN, Spi Mathis CA, DeKosky ST, Morris JC Inverse relation between *in vivo* am cerebrospinal fluid Abeta42 in hu 512-519.

[6] Dubois B, Feldman HH, Jacova C, Barberger-Gateau P, Cummings J, D, Gauthier S, Jicha G, Meguro K F, Robert P, Rossor M, Salloway Scheltens P (2007) Research criter Alzheimer's disease: Revising the teria. *Lancet Neurol* **6**, 734-746.

[7] Carter DA, Desmarais E, Bellis M Darpoux F, Brice A, Agid Y, Jailla (1992) More missense in amyloid g 256.

[8] Rossi G, Giaccone G, Maletta R, Mo Mangieri M, Giovagnoli AR, Bizzi Di Natale M, Tagliavini F, Bugiar A family with Alzheimer disease with A713T mutation of the APP 910-912.

[9] Conidi ME, Bernardi L, Puccio G, Curcio SA, Colao R, Piscopo P, Gall pane F, Clodomiro A, Mirabelli M Torchia G, Di Lorenzo R, Mandich RG, Bruni AC (2015) Homozygous mutation in an autosomal dominant ily. *Neurology* **84**, 2266-2273.

[10] Measso G, Cavarzeran F, Zappalá G TH, Pirozzolo FJ, Amaducci LA,

Psichiatria **4**, 477-506.

[15] Appollonio I, Leone M, Isella V, Piamarta F, Consoli T, Villa ML, Forapani E, Russo A, Nichelli P (2005) The Frontal Assessment Battery (FAB): Normative values in an Italian population sample. *Neurol Sci* **26**, 108-116.

[16] Caffarra P, Vezzadini G, Dieci F, Zonato A, Venneri A (2002) Una versione abbreviata del test di Stroop: Dati normativi nella popolazione italiana. *Nuova Riv Neurol* **12**, 111-115.

[17] Caffarra P, Vezzadini G, Dieci F, Zonato F, Venneri A (2002) Rey-Osterrieth complex figure: Normative values in an Italian population sample. *Neurol Sci* **22**, 443-447.

[18] Kaufer DI, Cummings JL, Ketchel P, Smith V, MacMillan A, Shelley T, Lopez OL, DeKosky ST (2000) Validation of the NPI-Q, a brief clinical form of the Neuropsychiatric Inventory. *J Neuropsychiatry Clin Neurosci* **12**, 233-239.

[19] Katz S, Ford AB, Moskowitz RW, Jackson BA, Jaffe MW (1963) Studies of illness in the aged. The index of ADL: A standardized measure of biological and psychosocial function. *JAMA* **185**, 914-919.

[20] Scheltens P, Barkhof F, Leys D, Pruvo JP, Nauta JJ, Vermersch P, Steinling M, Valk J (1992) Atrophy of medial temporal lobes on MRI in "probable" Alzheimer's disease and normal ageing: Diagnostic value and neuropsychological correlates. *J Neurol Neurosurg Psychiatry* **55**, 967-972.

[21] Pasquier F, Leys D, Weerts JGE, Mounier-Vehier F, Barkhof F, Scheltens P (1996) Inter-and intraobserver reproducibility of cerebral atrophy assessment on MRI scans with hemispheric infarcts. *Eur Neurol* **36**, 268-272.

[22] Fazekas F, Chawluk JB, Alavi A, Hurtung HI, Zimmerman RA (1987) MR signal abnormalities at 1.5 T in Alzheimer's dementia and normal aging. *Am J Roentgenol* **149**, 351-356.

[23] Nacmias B, Piaceri I, Bagnoli S, Tedde A, Piacentini S, Sorbi S (2014) Genetics of Alzheimer's disease and frontotemporal dementia. *Curr Mol Med* **14**, 993-1000.

[24] Zhan XH, Zha GC, Jiao JW, Yang LY, Zhan XF, Chen JT, Xie DD, Eyi UM, Matesa RA, Obono MM, Ehapo CS, Wei EJ, Zheng YZ, Yang H, Lin M (2015) Rapid identification of apolipoprotein E genotypes by high-resolution melting analysis in Chinese Han and African Fang populations. *Exp Ther Med* **9**, 469-475.

[25] Duits FH, Teunissen CE, Bouwman FH, Visser PJ, Mattsson N, Zetterberg H, Blennow K, Hansson O, Minthon L, Andreasen N, Marcusson J, Wallin A, Rikkert MO, Deramecourt V, Lebert F, Pijnenbu F, Grafman J, Cappa SF, Freedman BL (2011) Sensitivity of revised di behavioural variant of frontotempor 2456-2477.

[28] Giaccone G, Rossi G, Morbin M, T Bruni A (2002) A713T mutation c ian family with Alzheimer disease angiopathy. *Neurobiol Aging* **23**(Su

[29] Bernardi L, Geracitano S, Colao Anfossi M, Frangipane F, Curcio Tomaino C, Vasso F, Smirne N, (2009) AβPP A713T mutation in disease with cerebrovascular lesion 383-389.

[30] Guerreiro RJ, Baquero M, Blesa Bullido MJ, Calado A, Crook R, Gómez-Isla T, Hernández I, Lleó A, Lage P, Masdeu J, Molina-Porcel L, Pérez-Tur J, Relvas R, Oliveira CR, Sa A, Samaranch L, Sánchez-Valle Singleton A, Hardy J, Clarimón J (2 of Alzheimer's disease genes in Iber yields novel mutations in presenili *Aging* **31**, 725-731.

[31] Cruts M, Theuns J, Van Broeckh specific mutation databases for n diseases. *Hum Mutat* **33**, 1340-134

[32] Kinoshita J, Clark T (2007) Alzfor **401**, 365-381.

[33] Stenson PD, Mort M, Ball EV, Shav DN (2014) The Human Gene Mutat a comprehensive mutation repositor ular genetics, diagnostic testing an medicine. *Hum Genet* **133**, 1-9.

[34] Schöll M, Wall A, Thordardottir S, N, Långström B, Almkvist O, Graf Low PiB PET retention in preser biomarkers in Arctic APP mutation 229-236.

[35] Tomiyama T, Nagata T, Shimada H A, Kanemitsu H, Takuma H, Ku Ataka S, Wada Y, Yoshioka E, Ni Mori H (2008) A new amyloid var ization in Alzheimer's-type dem 377-387.